Protocol Synopsis Title

A Phase II study, randomized, controlled, efficacy assessor blinded, multi-center, international prospective study to assess the safety and effectiveness of Medi-Tate i-Temporary Implantable Nitinol Device (iTIND) in subjects with symptomatic Benign Prostatic Hyperplasia (BPH)

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Synopsis

TITLE: A Phase II, randomized, controlled, efficacy assessor blinded, multi-center, international prospective study to assess the safety and effectiveness of Medi-Tate i-Temporary Implantable Nitinol Device (iTIND) in subjects with symptomatic Benign Prostatic Hyperplasia (BPH)

PROTOCOL NUMBER: MT-03

INVESTIGATIONAL PRODUCT: Medi-Tate i-Temporary Implantable Nitinol Device (iTIND)

PHASE: II

INDICATION: Subjects with symptomatic BPH

STUDY OBJECTIVES: The study objectives are to demonstrate the efficacy and safety of the Medi-Tate iTIND as compared to control group (catheter only).

Population: Up to 190 subjects may be enrolled in the study in order to obtain a sample population of 170 randomized subjects with symptomatic BPH.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

Subjects must meet all of the inclusion criteria listed below to be eligible for randomization into the study:

1. Subject signed informed consent form (ICF)
2. Age 50 and above
3. Male with symptomatic BPH.
4. IPSS symptom severity score ≥ 10
5. Peak urinary flow of < 12 ml/sec . Meeting the criterion on (2) two separate voiding trials , on a minimum voided volume of at least 125 cc for each voiding trial.
6. Prostate volume between 25 ml to 75 ml (assessed by ultrasound)
7. Blood CBC and biochemistry up to two weeks before screening demonstrating: Normal values of the PT, PTT and INR tests (anticoagulants should be stopped according to GCP)
8. Subject able to comply with the study protocol
9. Normal Urinalysis and urine culture

Exclusion Criteria:

Subjects with any one of the exclusion criteria listed below will not be eligible for randomization into the study:

10. Cardiac arrhythmias, cardiac disease including congestive heart failure, uncontrolled diabetes mellitus, significant respiratory disease, or known immunosuppression;
11. Neurogenic bladder and/or sphincter abnormalities due to Parkinson's disease, multiple sclerosis, cerebral vascular accident, diabetes
12. A post void residual (PVR) volume > 250 ml measured by ultrasound or acute urinary retention
13. Compromised renal function (i.e., serum creatinine level > 1.8 mg/dl, or upper tract

disease);

14. Confirmed or suspected bladder cancer;
15. Recent (within 3 months) cystolithiasis or hematuria;
16. Urethral strictures, bladder neck contracture, urinary bladder stones or other potentially confounding bladder pathology;
17. An active urinary tract infection.
18. Enrolled in another treatment trial for any disease within the past 30 days.
19. Previous colo- rectal surgery (other than hemorrhoidectomy) or history of rectal disease if the therapy may potentially cause injury to sites of previous rectal surgery, e.g., if a transrectal probe is used;
20. Previous pelvic irradiation, cryosurgery or radical pelvic surgery;
21. Previous prostate surgery, balloon dilatation, stent implantation, laser prostatectomy, hyperthermia, or any other invasive treatment to the prostate
22. History of prostatitis within the past 5 years.
23. Median lobe obstruction of the prostate.
24. Cancer that is not considered cured, except basal cell or squamous cell carcinoma of the skin (cured defined as no evidence of cancer within the past 5 years).
25. Any serious medical condition likely to impede successful completion of the study
26. Participating in any other investigational study for either drug or device which can influence collection of valid data under this study.
27. Subjects who are actively taking medications that affects urination and BPH symptoms not completing the required washout period.
28. Baseline PSA ≥ 10 ng/ml.
29. Positive DRE.
30. Baseline PSA between 2.5–10 ng/ml and free PSA < 25%, without a subsequent negative prostate biopsy.

For clarification, a subject with a baseline PSA < 2.5 ng/ml or a subject with a baseline PSA between 2.5–10 ng/ml and free PSA ≥ 25% will not require additional testing and may be enrolled if the remaining inclusion/exclusion criteria are satisfied.

Intraoperative Exclusion Criteria:

31. Any abnormal findings on cystoscopy at the time of implantation (iTIND group) that would be inconsistent with the diagnosis of BPH.

STUDY DESIGN, DURATION AND PROCEDURES:

Up to 190 subjects will be enrolled in the study in order to obtain a sample population of 170 randomized subjects.

Study duration is 12 months and includes 7 visits.

DEVICE/TREATMENT AND ROUTE OF ADMINISTRATION:

iTIND Device will be implanted for 5-7 days. Sham will be a routine Foley catheter placement and removal procedure conducted at the implantation visit and at the device retrieval visit.

SAFETY VARIABLES:

- Incidence (% of patients) and frequency (no. of events) of device related adverse events
- Incidence (% of patients) and frequency (no. of events) of any adverse events
- Safety laboratory measurements
- Vital signs and physical examinations

EFFICACY VARIABLES:

Primary Endpoint:

The primary efficacy endpoints for this study are:

- Change from baseline to month 3 in the IPSS/ AUA-SI Score. Analysis will compare the differences between the two study groups.
- Change from baseline to month 12 in the IPSS/ AUA-SI Score. Analysis will assess the within iTIND group change.

Secondary Endpoints:

Analysis will compare the differences between groups in:

- Change from baseline to month 3 in IIEF (International Index of Erectile Function),
- Change from baseline to month 3 in SHIM (Sexual Health Inventory for Men)
- Change from baseline to month 3 in Qmax (maximum urinary flow rate)
- Change from baseline to month 3 in PVR (post-void residual urine volume),

STATISTICAL METHODOLOGY:

A total of 170 subjects randomized to treatment with either iTIND arm or to the control arm using a respective randomization scheme of 2:1 are expected to be recruited into this trial. Since it is anticipated that some of the participating sites will recruit an insufficient number of subjects to allow estimation of within sites effect size or treatment by site interaction study centers will be pooled into Country/Geographical Region (CGR).

Randomization:

Subjects will be randomized using a 2:1 assignment ratio to either iTIND group or to the control group, respectively. Randomization will employ permuted blocks stratified by center.

Overall Significance Level:

The overall significance level for this study will be 5% using two-tailed tests. To preserve the overall type-I error of the study the following will take place:

- The study identifies two primary endpoints and four secondary end-points ordered in a hierarchy.
- Meeting both primary endpoints at type-I error of 5% each, is sufficient to determine study success in demonstrating the effectiveness and effect durability of iTIND treatment.
- Secondary endpoints will be tested only if both primary endpoints are met.
- Type-I error control for multiple endpoints testing will utilize the gate keeping approach performed according to the following hierarchy order:

1. Change from baseline to month 3 in IIEF (International Index of Erectile Function)
2. Change from baseline to month 3 in SHIM (Sexual Health Inventory for Men)
3. Change from baseline to month 3 in Qmax (maximum urinary flow rate)
4. Change from baseline to month 3 in PVR (post-void residual urine volume)

Sample Size Rationale

Study power was estimated for both primary endpoints to ensure that study is adequately powered to meet both endpoints.

The first primary endpoint for this study is the change from baseline to month 3 in the IPSS/ AUA-SI score and analysis is planned to compare the changes of both study arm. The power of the trial for this endpoint was estimated based the following assumptions for that primary endpoint:

- The expected STD of the 3-month change from baseline for the 2 study arm is 7.35 IPSS/ AUA-SI points.
- The expected effect size (difference between the changes in the iTIND arm and the control arm) is 4 IPSS/ AUA-SI points.
- A two-sample t-test employing a 5% two-tailed testing was used to estimate study power.
- Analysis suggested that for an expected effect size of 4 IPSS/ AUA-SI points, STD of change of 7.35 IPSS/ AUA-SI points, using a 5% two-tailed testing, a total of 170 subjects randomized to either iTIND group or the control using a respective randomization scheme of 2:1 will provide a power of 87.7% for this endpoint.

The second primary endpoint for this study is the change from baseline to month 12 in the IPSS/ AUA-SI score and analysis will assess the within iTIND group change. The power of the trial for this endpoint was estimated based the following assumptions:

- The expected mean 12-month change and STD of the 12-month change from baseline for the iTIND arm are 4.0 and 7.35 IPSS/ AUA-SI points, respectively.
- Endpoint will be met if the lower bound of the two-sided 95% confidence interval for that 12-month mean change from baseline calculated for the iTIND arm will be higher than 1 IPSS/ AUA-SI point reflecting a 25% boundary as compared to the expected mean effect size (4.0 IPSS/ AUA-SI points).
- A two-sided 95% confidence interval for the 12-month change from baseline within the iTIND arm was used to estimate study power.
- Analysis suggested that for the 12-month change analysis of the iTIND arm a total of 100 subjects will provide a power of 97.8% for this endpoint.

Principal Analysis of the Two Primary Endpoints

- Subjects prescribed with alpha blockers or with 5-ARIs following initiation of study treatment and up to the period that ends at 12-month follow-up visit will be considered, for the purpose of statistical analysis, as treatment failures starting from the date in which these medications were administered. To account for this potential source of bias in the analysis, all IPSS/AUA-SI measurements of an individual subject, starting from the date of initiation of alpha blockers or 5-ARIs administration will be imputed to be their baseline values.
- The principle analysis of the two primary endpoints will be performed for the ITT analysis

set. The statistical model to be used for inference of the two primary endpoints will be a repeated measures model (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical month in trial by treatment interaction and baseline IPSS/AUA-SI measurement as one degree of freedom covariate. The unstructured covariance matrix for repeated observations within subjects will be used. In case that the model will not converge, the Maximum-Likelihood (ML) estimation method will be used instead of the default Restricted ML (REML). If the model still does not converge then a simpler covariance structures with less parameters will be used, according to the following order: Heterogeneous Autoregressive(1) (ARH(1)), Heterogeneous Compound Symmetry (CSH), Autoregressive(1) (AR(1)), and Compound Symmetry (CS).

- The Least Square Means (LSM) at Month 3 visit of the change from baseline will be compared between the iTIND arm and the control group and will be used for inference regarding the first primary endpoint.
- The Least Square Means (LSM) at Month 12 visit of the change from baseline within the iTIND arm will be used for inference regarding the second primary endpoint. In the case that the Lower CI of the Least Squares Means SAS table will be higher than 1 IPSS/ AUA-SI score point then a positive inference will be made regarding the second primary endpoint.
- Study will be considered positive if both primary endpoints are met.
- To assess the robustness of results and conclusions and the potential impact of missing values a comprehensive set of sensitivity analysis will be performed.

Statistical Analysis Plan (SAP)

The study will be conducted when the Sponsor and the Biostatistician assigned to the study are fully blinded to treatment assignment. A more detailed SAP will be developed by the statistician prior to revealing of the study blind.

I. STATISTICAL METHODOLOGY

A total of 170 subjects randomized to treatment with either iTIND arm or to the control arm using a respective randomization scheme of 2:1 are expected to be recruited into this trial. Since it is anticipated that some of the participating sites will recruit an insufficient number of subjects to allow estimation of within sites effect size or treatment by site interaction study centers will be pooled into Country/Geographical Region (CGR).

A. RANDOMIZATION PROCEDURE

Subjects will be randomized using a 2:1 assignment ratio to either iTIND group or to the control group, respectively. Randomization will employ permuted blocks stratified by center.

B. SAMPLE SIZE RATIONALE

Study power was estimated for both primary endpoints to ensure that study is adequately powered to meet both endpoints.

The first primary endpoint for this study is the change from baseline to month 3 in the IPSS/ AUA-SI score and analysis is planned to compare the changes of both study arms. The power of the trial for this endpoint was estimated based the following assumptions for that primary end-point:

- The expected STD of the 3-month change from baseline for the 2 study arm is 7.35 IPSS/ AUA-SI points.
- The expected effect size (difference between the changes in the iTIND arm and the control arm) is 4 IPSS/ AUA-SI points.
- A two-sample t-test employing a 5% two-tailed testing was used to estimate study power.
- Analysis suggested that for an expected effect size of 4 IPSS/ AUA-SI points, STD of change of 7.35 IPSS/ AUA-SI points, using a 5% two-tailed testing, a total of 170 subjects randomized to either iTIND group or the control using a respective randomization scheme of 2:1 will provide a power of 87.7% for this endpoint.

The second primary endpoint for this study is the change from baseline to month 12 in the IPSS/ AUA-SI score and analysis will assess the within iTIND group change. The power of the trial for this endpoint was estimated based the following assumptions for that primary end-point:

- The expected mean 12-month change and STD of the 12-month change from baseline for the iTIND arm are 4.0 and 7.35 IPSS/ AUA-SI points, respectively.
- Endpoint will be met if the lower bound of the two-sided 95% confidence interval for that 12-month mean change from baseline calculated for the iTIND arm will be higher than 1

IPSS/ AUA-SI point reflecting a 25% boundary as compared to the expected mean effect size (4.0 IPSS/AUA-SI points).

- A two-sided 95% confidence interval for the 12-month change from baseline within the iTIND arm was used to estimate study power.
- Analysis suggested that for the 12-month change analysis of the iTIND arm a total of 100 subjects will provide a power of 97.8% for this endpoint.

C. OVERALL SIGNIFICANCE LEVEL

The overall significance level for this study will be 5% using two-tailed tests. To preserve the overall type-I error of the study the following will take place:

- The study identifies two primary endpoints and four secondary end-points ordered in a hierarchy.
- Meeting both primary endpoints at type-I error of 5% each, is sufficient to determine study success in demonstrating the effectiveness and effect durability of iTIND treatment.
- Secondary endpoints will be tested only if both primary endpoints are met.
- Type-I error control for multiple endpoints testing will utilize the gate keeping approach performed according to the following hierarchy order:
  1. Change from baseline to month 3 in IIEF (International Index of Erectile Function)
  2. Change from baseline to month 3 in SHIM (Sexual Health Inventory for Men)
  3. Change from baseline to month 3 in Qmax (maximum urinary flow rate)
  4. Change from baseline to month 3 in PVR (post-void residual urine volume)

D. EFFICACY ENDPOINTS AND ANALYSES

The study identifies two primary endpoints and four secondary end-points ordered in a hierarchy for significance testing as provided below.

a. Primary Endpoints

The two primary efficacy endpoints for this study which are given in the hierarchy order of significance testing for are:

1. Change from baseline to month 3 in the IPSS/ AUA-SI Score. Analysis will compare the differences between the two study groups.
2. Change from baseline to month 12 in the IPSS/ AUA-SI Score. Analysis will assess the within iTIND group change.

b. Secondary Endpoints

Secondary endpoints will be tested only if both primary endpoints are met. Analysis will compare the differences between groups at month 3 and significance testing will be performed, utilize the gate keeping approach, according to the hierarchy order outlined below:

1. Change from baseline to month 3 in IIEF (International Index of Erectile Function),
2. Change from baseline to month 3 in SHIM (Sexual Health Inventory for Men)
3. Change from baseline to month 3 in Qmax (maximum urinary flow rate)
4. Change from baseline to month 3 in PVR (post-void residual urine volume),

E. ANALYSIS SETS

a. Intent-to-Treat (ITT) Analysis Set

The intent-to-treat (ITT) population will include all randomized patients according to treatment subjects were randomized to regardless of treatment they actually received.

b. Safety (ST) Analysis Set

The safety population will include all randomized patients who initiated study treatment procedures according to treatment actually administered.

c. 3-Months Completer Analysis Set (CO3M)

The 3-Month completer analysis set (CO_{3M}) will consist of all subjects who complete the 3 months comparative phase of the study.

Note: Subjects who are excluded intra-operatively due to abnormal findings on cystoscopy will not be included in the analysis populations outlined above. Any such exclusions will be reported, including demographics, baseline characteristics and reasons for exclusion.

F. DEMOGRAPHIC BASELINE CHARACTERISTICS ANALYSIS

Demographic and baseline data will be performed for the ITT analysis set. Subject demographic and baseline characteristics, including BPH prognostic factors will be examined to assess the comparability of the treatment groups. Medical history, Prior medications, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median, minimum, and maximum) will be provided. For

categorical variables, subject counts and percentages will be provided. Categories for missing data will be presented if necessary.

G. PLANNED METHOD OF ANALYSIS

All formal pre-defined significance testing will be performed for the ITT Analysis Set.

a. Principal Analysis of the Two Primary Endpoints

- Subjects prescribed with alpha blockers or with 5-ARIs following initiation of study treatment and up to the period that ends at 12-month follow-up visit will be considered, for the purpose of statistical analysis, as treatment failures starting from the date in which these medications were administered. To account for this potential source of bias in the analysis, all IPSS/AUA-SI measurements of an individual subject, starting from the date of initiation of alpha blockers or 5-ARIs administration will be imputed to be their baseline values.
- The statistical model to be used for inference of the two primary endpoints will be a repeated measures model (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical month in trial by treatment interaction and baseline IPSS/AUA-SI measurement as one degree of freedom covariate. The unstructured covariance matrix for repeated observations within subjects will be used. In case that the model will not converge, the Maximum-Likelihood (ML) estimation method will be used instead of the default Restricted ML (REML). If the model still does not converge then a simpler covariance structures with less parameters will be used, according to the following order: Heterogeneous Autoregressive(1) (ARH(1)), Heterogeneous Compound Symmetry (CSH), Autoregressive(1) (AR(1)), and Compound Symmetry (CS).
- The Least Square Means (LSM) at Month 3 visit of the change from baseline will be compared between the iTIND arm and the control group and will be used for inference regarding the first primary endpoint.
- The Least Square Means (LSM) at Month 12 visit of the change from baseline within the iTIND arm will be used for inference regarding the second primary endpoint. In the case that the Lower CI of the Least Squares Means SAS table will be higher than 1 IPSS/ AUA-SI score point then a positive inference will be made regarding the second primary endpoint.
- Study will be considered positive if both primary endpoints are met.

b. Sensitivity Analysis of the Two Primary Endpoints

i. Types Of Missing Values

Before revealing of the blind, missing observations will be classified according to the following three types of missing values which are defined according to the relation of the missingness mechanism to observed and unobserved data:

- Missing Completely At Random (MCAR): If the missing value reason deemed unrelated to the observed or to the unobserved IPSS/AUA-SI score
- Missing At Random (MAR): If the missing value reason deemed as possibly related to the observed pattern of IPSS/AUA-SI outcome and measurement was taken at Termination visit. For example: Subjects early terminated the study due to adverse event or withdrew consent but performed early termination visit and his IPSS/AUA-SI score was recorded.
- Missing Not At Random (MNAR): If the missing value reason could not be deemed as unrelated to unobserved data, the missing data will be classified as Missing Not At Random. This category includes: lost to follow-up, informed consent withdrawal or withdrawal due to adverse event without IPSS/AUA-SI measurement being taken at termination date.

ii. Assessment of the Impact of Missing Data Assuming MCAR or MAR

The use of repeated measures mixed-effects model is considered adequate and unbiased under Missing Completely At Random (MCAR) and Missing At Random (MAR) missingness mechanisms.

iii. Assessment of the Impact of Missing Data Assuming NMAR

In addition to the above, any missing data that will be classified as NMAR will be treated as reflecting treatment failure and will be assigned a zero change from baseline and analysis will be repeated using this imputed value.

iv. Comparison of the Primary Analysis Results on Different pre-defined Data Analysis Set

The results of the primary analysis on the ITT analysis set will be compared to the results on the CO_{3M} analysis set.

v. Responder Analysis

The ITT analysis set will further be used to compare the 3-months responder rate between the two study groups in the first primary endpoint. A subject will be defined as a treatment responder in the case that the 3-month improvement from four effects: treatment group and baseline IPSS/AUA-SI will be used to test the between groups differences.

c. Secondary Endpoint Analyses

The statistical model to be used for the analysis of the change from baseline to month 3 for all secondary endpoints will be a repeated measures model (SAS® MIXED procedure with REPEATED sub-command). The model will include the following fixed effects: categorical month in trial by treatment interaction and baseline measurement of the tested parameter as a one degree of freedom covariate. The unstructured covariance matrix for repeated observations within subjects will be used. In case that the model will not converge, the Maximum-Likelihood (ML) estimation method will be used instead of the default Restricted ML (REML). If the model still does not converge then a simpler covariance structures with less parameters will be used, according to the following order: Heterogeneous Autoregressive(1) (ARH(1)), Heterogeneous Compound Symmetry (CSH), Autoregressive(1) (AR(1)), and Compound Symmetry (CS). The Least Square Means (LSM) at Month 3 visit of the change from baseline will be compared between the iTIND arm and the control group and will be used for inference regarding the first primary endpoint.

H. SAFETY ASSESSMENTS

a. Adverse Events

The incidence (no. of subjects) and frequency (no. of events) of adverse events will be presented by System Organ Class and preferred terminology according to MedDRA dictionary. Data will be tabulated by treatment group, gender, age, and all of AEs attributes. Serious adverse events and seriousness criteria will be listed and discussed on a case by case basis. Summary tables of pre-defined selected AEs (e.g. device related events) which will be identified prior to revealing of the blind will also be provided.

b. Laboratory Tests

Descriptive statistics of quantitative tests results and changes from baseline by scheduled visit and treatment group are provided. Listings and summary tables of the clinically significant laboratory results will be generated and presented by study group.

c. Vital Signs

Descriptive statistics of tests results and changes from baseline by scheduled visit and treatment group are provided. Listings and summary tables of the clinically significant vital signs measurements will be generated and presented by study group. Shift analysis from baseline will be provided as well.

d. Tolerability Assessments

Tolerability analysis will be based on the number (%) of subjects who failed to complete the study, the number (%) of subjects who failed to complete the study due to adverse events. Time to withdrawal will be presented by Kaplan-Meier curves. Significance testing of time to withdrawal will be done using Cox's proportional hazards model.

I. INTERIM ANALYSES

No interim analysis is planned for this study.